Staging of the Mediastinum
Are We Already There?

Wilfried Ernst Erich Eberhardt, MD, and Rodrigo Hepp, MD†*

In this month's edition of the *Journal of Thoracic Oncology*, Farjah et al.[1] present a "prediction model for pathologic N2 disease in lung cancer patients with negative mediastinum by PET/CT," where PET/CT refers to positron emission tomography/computed tomography. The background for their investigation is the fact that a clear algorithm currently exists on how to proceed with positive PET/CT findings on initial staging investigations in suspected locally advanced non–small-cell lung cancer (NSCLC).[2] However, more loose guidelines exist in the case of both CT- and PET/CT-negative evaluation of the mediastinal nodes, and institutional policies for this situation differ considerably. They present here a very large, single-institutional cohort study on 938 patients from Memorial Sloan Kettering Cancer Center in New York, reporting on a rather homogeneous group of patients with T1 and T2 primary lesions on CT scans and PET-CT findings of N0 or N1.[1] Patients were planned for curative resection, but invasive mediastinal staging was implemented only selectively based on the individual decision by the handling surgeon in patients where clinical factors were suggestive of high risk of occult N2 disease in the mediastinum. Of all 938 patients overall 9.9% were diagnosed as having N2 nodes infiltrated by tumor, but only in nine these were detected with invasive mediastinal staging whereas in 84 patients N2 disease was only confirmed pathologically based on the findings in the resected specimen and mediastinal nodes from mediastinal lymph node sampling/dissection at the time of surgery. In nine patients the preoperative invasive staging procedure showed finally to be a false-negative result, giving a sensitivity of 50% for this procedure. Farjah et al. point out that in most cases the indication to perform an invasive mediastinal staging is based on an individual, rather subjective, decision by the responsible surgeon. This is typically relying on some clinical characteristics such as central location of the primary and hilar lymph node involvement, which are more or less indicative of a high risk of mediastinal disease. Their aim was clearly to develop more objective and reproducible criteria for predicting the positivity of lymph nodes in the mediastinum, based on some risk factors that are available before surgery and that have already been described in the literature and could be evaluated here in all analyzed patients of this homogeneous patient cohort.[3]

Six factors were finally included to this investigation: tumor location—central versus peripheral—and tumor size based on initial CT scans, extent of nodal disease by CT, maximum standardized uptake value (SUV_{max}) of the primary tumor in PET, N1-disease by PET and tumor histopathology. These six parameters had been previously described to be significantly associated with the risk of N2 involvement to be revealed at the time of surgery.[3] The authors of the discussed manuscript used a complex logistical regression model and also implemented a development set (about two third of the population) and a validation set for the model (about one third of the population).

Although initial univariate analyses showed significant association between increased tumor size, nodal status by CT, SUV_{max} of the primary tumor, N1 by PET on one side and N2

*Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany; and †Department of Radiation Oncology, Evangelisches Krankenhaus Gelsenkirchen, Gelsenkirchen, Germany
Disclosure: The authors declare no conflict of interest.
Address for correspondence: Wilfried Ernst Erich Eberhardt, MD, University of Essen Medical School, West German Cancer Center, Hufeland Strasse 55, Essen, Germany, 45122. E-mail: wilfried.eberhardt@uni-essen.de

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status proven at the time of surgery on the other, only the latter of the factors turned out to be significant in the following multivariate predictive model. So the final predictive model was based on "PET findings of N1 disease" as the only remaining important parameter in the model. Evaluation of this predictive model by *C statistic* and *goodness-of-fit* showed it to be performing reasonably well. The authors conclude from their findings that this result can in the future be used to guide further research on the development of objective prediction models for N2 disease in the mediastinum. Again, in comparison to the rather subjective decision making by individual thoracic surgeons of a single or even several different institutions, this parameter-guided most objective approach offers several advantages. Besides allowing thoracic surgeons to move away from subjective decision making, such data sets could also help to rationally reduce patient risks as well as costs related to unnecessary invasive staging methods in early or locally advanced NSCLC.[1]

We will not cover the issues related to the development of the new technologies such as endobronchial ultrasound and endoesophageal ultrasound for the invasive staging of the mediastinum here, although they have important implications on the whole staging algorithm as it is currently developing.[3] This is of major importance, especially in patients who are candidates for nonsurgical procedures, such as stereotactic body radiotherapy, and in these situations a false-negative rate of predicting mediastinal involvement of 50% is clearly not acceptable.

Can predictive models help to completely substitute experienced clinical decision making in locally advanced NSCLC? The answer is probably both—yes and no—and no final statement is currently possible on this controversy.

One of the main issues with stage III disease in NSCLC is the existing heterogeneity of patients not only based on staging including mediastinal involvement, but also on the comorbidity profiles of the patients and even more with the available permutations of multimodality treatment approaches that could potentially be performed in the setting of the individual patient.[4] Examples for these important influences may be seen in the lung function in the individual patient, which determine any aggressive local approach whether it is surgery on the one hand or definitive chemoradiation on the other. Another good example is the problem that adjuvant chemotherapy after extended resections (e.g., pneumonectomies) may be rather risky and alternatively, in these patients, induction chemotherapy followed by definitive surgery may be much easier and less risky to the patients regarding infectious complications during chemotherapy. But these situations are only relevant typically for small subsets of patients and, unfortunately for these small subsets, little evidence from larger patient groups or trials is currently available in the literature.

Can we change this dilemma? Only if more stage III patients would be treated in prospective randomized trials in the future! Deriving data from large retrospective data sets from single institutions as the one presented in this article is an important contribution to the "current body of evidence" in this setting and the authors can only be congratulated for including nearly 1000 patients from 2004 to 2009 in this detailed analyses and for having all the necessary parameters documented in the patient cohort.

However, the next step for us all should be to routinely treat all curatively intended patients in prospective clinical trials (preferably also controlled ones). We are realistic—this is more of wishful thinking—the current reality bites very, very hard. . . Only a few prospective randomized clinical trials in stage III have been performed within the recent years! We will need a joint effort by large national or even international study groups to speed up clinical research for these curative situations with highest needs for clinical evidence. Recent developments with the large International Association for the Study of Lung Cancer staging project and with the European Thoracic Oncology Platform projects in Europe are highlight platforms for this important diagnostic as well as therapeutic workup of large enough patient groups to help us further develop the diagnostic and therapeutic options for the individual NSCLC patient![5,6]

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